CLAIMS

1. A method for treatment or prophylaxis of disease caused by deficiency, in a subject, of an enzyme belonging to the heme biosynthetic pathway, the method comprising administering, to the subject, an effective amount of a catalyst which is said enzyme or an enzymatically equivalent part or analogue thereof.

2. A method according to claim 1, wherein the disease is selected from the group consisting of
acute intermittent porphyria (AIP),
ALA deficiency porphyria (ADP),
Porphyria cutanea tarda (PCT),
Hereditary coproporphyria (HCP),
Harderoporphyria (HDP),
Variegata porphyria (VP),
Congenital erythropoetic porphyria (CEP),
Erythropoietic protoporphyria (EPP), and
Hepatoerythropoietic porphyria (HEP).

3. A method according to claim 1 ~~or 2~~, wherein the catalyst is an enzyme selected from the group consisting of
porphobilinogen deaminase (PBGD)
ALA dehydratase,
Uroporphyrinogendecarboxylase,
Coproporphyrinogen oxidase,
Coproporphyrinogen oxidise,
Protoporphyrinogen oxidase,
Uroporphyrinogen III synthase,
Ferrochelatase, and
Uroporphyrinogen decarboxylase,
or an enzymatically equivalent part or analogue thereof.

4. A method according to ~~any of the preceding claims~~ claim 1, wherein the disease is AIP and the enzyme is PBGD or an enzymatically equivalent part or analogue thereof.

5. A method according to ~~any of the preceding claims~~ Claim 1, wherein the catalyst is a recombinant form of the enzyme belonging to the heme biosynthetic pathway or of the enzymatically equivalent part or analogue thereof.

6. A method according to ~~any of the preceding claims~~ Claim 1, wherein the catalyst is administered by a route selected from the group consisting of the intravenous route, the intraarterial route, the intracutaneous route, the subcutaneous route, the oral route, the buccal route, the intramuscular route, the anal route, the transdermic route, the intradermal route, and the intratechal route.

7. A method according to ~~any of claims 1-6~~ Claim 1, wherein the catalyst is formulated in an isotonic solution, ~~such as 0.9% NaCl and 10-50 mM Sodium phosphate pH 6.50 to 8- or Sodium phosphate, glycine, mannitol or the corresponding potassium salts.~~

8. A method according to ~~any of claims 1-7~~ Claim 1, wherein the catalyst is lyophilised.

9. A method according to ~~any of claims 1-8~~ Claim 1, wherein the catalyst is sterile filtered.

10. A method according to ~~any of claims 1-6, 8 or 9,~~ Claim 1 wherein the catalyst is formulated as lipid vesicles comprising phosphatidylcholine or phosphatidylethanolamine or combinations thereof.

11. A method according to ~~any of claims 1-6, 8 or 9,~~ Claim 1 wherein the catalyst is incorporated into erythrocyte ghosts.

12. A method according to ~~any of claims 1-6, 8 or 9,~~ Claim 1 wherein the catalyst is formulated as a sustained release formulation ~~involving~~ comprising biodegradable microspheres, ~~such as microspheres comprising polylactic acid, polyglycolic acid or mixtures of these.~~

13. A method according to ~~any of claims 1-9,~~ Claim 1 wherein the catalyst is lyophilized in a two-compartment cartridge, where the catalyst will be in the front compartment and water for reconstitution in the rear compartment.

14. A method according to claim 13, wherein the two compartment cartridge is combined with an injection device to administer the catalyst either by a needle or by a needle-less (high pressure) device.

15. A method according to ~~any of claims~~ claim 1 ~~-9,~~ wherein the catalyst is formulated in a physiological buffer containing an enhancer for nasal administration.

16. A method according to ~~any of the preceding claims,~~ claim 1 wherein the catalyst is formulated as an oral formulation containing lipid vesicles, ~~such as those comprising phospatidylcholine, phosphatidylethanolamine, or sphingomyeline, or dextrane microspheres.~~

17. A method according to ~~any of the preceding claims~~ claim 1, wherein the catalyst is formulated so as to enhance the half-life thereof in the subject's bloodstream.

18. A method according to claim 17, wherein the catalyst has a polyethylene glycol coating.

19. A method according to claim 17, wherein the catalyst is complexed with a heavy metal.

20. A method according to ~~any of the~~ claim preceding ~~claims~~, wherein the catalyst is an enzymatically equivalent part or analogue of the enzyme and exerts at least part of its enzymatic activity intracellularly upon administration to the subject.

21. A method according to claim 20, wherein the catalyst is a small artificial enzyme or an organic catalyst which can polymerize porphobilinogen to hydroxymethylbilane

22. A method according to ~~any of claims~~ claim 1 ~~-9,~~ wherein the catalyst is said enzyme formulated in such a manner that it exerts at least part of its enzymatic activity intracellularly upon administration to the subject.

23. A method according to claim 22, wherein the catalyst is tagged with specific carbohydrates or other liver cell specific structures for specific liver uptake.

24. A method according to claims 1-~~19~~, wherein the catalyst exerts substantially all its enzymatic activity extracellularly in the bloodstream.

25. A method according to claim 24, wherein the enzymatic activity of the catalyst on its relevant heme precursor results in a metabolic product which 1) either moves into the intracellular compartment and is converted further via the remaining steps of the heme biosynthetic pathway or 2) is excreted from the subject via urine and/or faeces.

26. A method according to ~~any of the preceding claims~~ claim 1, wherein the catalyst has been prepared by a method comprising

a) introducing, into a suitable vector, a nucleic acid fragment which includes a nucleic acid sequence encoding the catalyst;
b) transforming a compatible host cell with the vector;
c) culturing the transformed host cell under conditions facilitating expression of the nucleic acid sequence; and
d) recovering the expression product from the culture
and optionally subjecting the expression product to post-translational processing, such as in vitro protein refolding, enzymatic removal of fusion partners, alkylation of amino acid residues, and deglycosylation, so as to obtain the catalyst.

27. A method according to ~~any of claims~~ claim 1-~~25~~, wherein the catalyst has been prepared by liquid-phase or solid-phase peptide synthesis.

28. A method according to ~~any of the preceding claims~~ claim 1, wherein the catalyst is free from any other biological material of human origin.

29. A method according to ~~any of the preceding claims~~ claim 1, wherein the catalyst is administered at least once a day, ~~such as 2, 3, 4, and 5 times daily.~~

30. A method according to ~~any of the preceding claims~~ claim 1 wherein the daily dosage is in the range of 0.01 – 1.0 mg/kg body weight per day, ~~such as in the range of 0.05 – 0.5 mg/kg body weight per day.~~

31. A method according to ~~any of the preceding claims~~ Claim 1, wherein the daily dosage is about 0.1 mg per kg body weight per day.

32. A catalyst which is an enzyme of the heme biosynthetic pathway or an enzymatically equivalent part or analogue thereof, ~~for use as a medicament~~ A pharmaceutical composition comprising.

33. Use of a catalyst which is an enzyme of the heme biosynthetic pathway or an enzymatically equivalent part or analogue thereof for the preparation of a pharmaceutical composition for the treatment or prophylaxis of diseases caused by deficiency of said enzyme.

34. The use according to claim 33, wherein the treatment or prophylaxis is performed according to any of claims 1-31.

35. A method according to ~~any of claims~~ Claim 1 ~~-31~~ wherein the catalyst is a recombinant form of the enzyme.

36. A method according to ~~any of claims~~ Claim 1 ~~-31~~ wherein the catalyst is recombinant human PBGD based on any of Seq. ID NO 1 (clone PBGD 1.1) and Seq. ID NO 12 (non-erythro PBGD 1.1.1).

~~36.~~ 37. A catalyst according to claim 32, which is recombinant human PBGD based on any of Seq. ID NO 1 (clone PBGD 1.1) and Seq. ID NO 12 (non-erythro PBGD 1.1.1).

~~37~~ 38. A method for treating a patient having a mutation in the PBGD gene causing an enzyme defect, comprising the use of a human PBGD cDNA sequence of either non-erythropoietic form or erythropoietic form according to the tissue in which PBGD should be expressed, and transfection of the patient with the relevant cDNA.

~~38~~ 39. The method according to claim 37 wherein the enzyme defiency is selected from enzyme defiencies resulting in a disease selected from Acute Intermittent Porphyria, (AIP), ALA deficiency porphyria (ADP), Porphyria cutanea tarda (PCT), Hereditary coproporphyria (HCP), Harderoporphyria (HDP), Variegata porphyria (VP), Congenital

erythropoietic porphyria (CEP), Erythropoietic protoporphyria (EPP), and Hepatoerythropoietic porphyria (HEP).

39. The method according to claim 39 wherein the disease is Acute Intermittent Porphyria, (AIP).

40. The method according to any of claims 37-39 wherein the human PBGD cDNA sequence is selected from Seq. ID NO 1 (clone PBGD 1.1) and Seq. ID NO 12 (non-erythro PBGD 1.1.1)

41. The method according to any of claims 37-40 wherein the transfection is by use of a vector selected from adenovirus, retrovirus and associated adenovirus.

42. The method according to any of claims 37-41 wherein the PBGD gene transfer vector into human cells (erythropoeitic and/or non-erythropoietic) results in normal PBGD activity.

43. A method of gene therapy treatment of patients with Acute Intermittent Porphyria (AIP) by a correction of one of the specific point mutations identified causing AIP by use of chimeraplasty gene repair.

44. The method according to any of claims 43 wherein the delivery system for transfection is by use of non-viral vectors formulated in a vehicle preparation comprisng one or more components selected from cationic phospholipids, phospholipids, phospholipids mixed with neutral lipids, lictosylated PEI, liposomes liposomes comprising mixtures of natural phopholipids and neutral lipids.

45. A method according to claim 43 or 44 wherein the mutation is selected from Table A.